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Assessment of Left Atrial Pressure–Area Relation in Humans by Means of Retrograde Left Atrial Catheterization and Echocardiographic Automatic Boundary Detection: Effects of Dobutamine

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Objectives. **This study sought to validate and apply a new method for obtaining the left atrial (LA) pressure–area relation.**

Background. **In physiologic investigations, the pressure–area relation is the most accurate and representative index of LA hemodynamic status.**

Methods. **We applied real-time two-dimensional echocardiographic imaging with automatic boundary detection to estimate LA area changes. To obtain LA pressure, a catheter-tipped micromanometer was introduced retrogradely into the left atrium using a steerable cardiac catheter developed at our institution. Twenty-five patients (11 normal subjects, 7 patients with an enlarged left atrium due to heart failure, 7 patients with atrial fibrillation) were studied before and after dobutamine administration. From the LA pressure–area relation, the area of the A loop (the first counterclockwise loop) and the V loop (the second clockwise loop), the pressure–minimal area relation and the LA passive elastic chamber stiffness constant were measured.**

Results. **Normalized pressure–minimal area relation was highly linear and sensitive to changes in inotropic state (normal subjects: from 0.96 to 1.27 mm Hg/cm^2, $p < 0.01$; patients with heart failure: from 0.59 to 0.68 mm Hg/cm^2, p = NS; patients with atrial fibrillation: from 0.80 to 1.06 mm Hg/cm^2, $p < 0.05$). The LA stroke work index was accurately calculated, and a very good correlation was found with LA preload. LA stroke work index was lower in patients with heart failure (3.9 ± 0.8 cm^2·mm Hg, $p < 0.001$), whereas the LA stiffness constant was increased in patients with heart failure (0.801 ± 0.097 cm^{-2}, $p < 0.01$) and atrial fibrillation (0.796 ± 0.091 cm^{-2}, $p < 0.01$) compared with normal subjects (stroke work index 7.3 ± 1.9 cm^2·mm Hg, stiffness constant 0.623 ± 0.107 cm^{-2}, respectively). In addition, increased inotropic state after dobutamine administration resulted in improved LA pump function (stroke work index) in normal subjects (from 10.2 ± 0.9 to 13.8 ± 1.9 cm^2·mm Hg, $p < 0.001$) and patients with heart failure (from 4.3 ± 0.4 to 7.6 ± 0.4 cm^2·mm Hg, $p < 0.001$), as well as in decreased stiffness constant in all groups of patients (normal subjects: from 0.712 ± 0.141 to 0.473 ± 0.089 cm^{-2}; patients with heart failure: from 0.896 ± 0.181 to 0.494 ± 0.093 cm^{-2}; patients with atrial fibrillation: from 0.779 ± 0.145 to 0.467 ± 0.086 cm^{-2}, $p < 0.001$).**

Conclusions. **The method described here is both safe and reproducible for obtaining the LA pressure–area relation. LA function is impaired in patients with heart failure and in those with atrial fibrillation and may be acutely improved with inotropic agents in both normal and diseased atria.**

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Invasive and noninvasive methods have been used for assessing atrial function (1–5). In physiologic investigations, the study of the pressure–area relation is the most accurate and representative index of the hemodynamic conditions that exist in cardiac chambers (4–7). However, the left atrial (LA) pressure–area relation has not been adequately studied, mainly because of the difficulties encountered with the transseptal technique of LA catheterization, which results in interatrial septal injury (8). Retrograde nontransseptal access to the left atrium may be achieved consistently and safely by using a steerable LA catheter developed at our institution (9–11). Furthermore, only recently has an accurate method of determining area changes by means of automatic boundary detection (ABD) two-dimensional echocardiography been developed (12,13). Therefore, the present study sought to obtain the LA pressure–area relation in normal subjects, in patients with heart failure due to ischemic heart disease and in patients with atrial fibrillation and to study the response to dobutamine administration.

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Abbreviations and Acronyms

ABD = automatic boundary detection
dA/dt = first derivative of left atrial area change
E_m = elastance at minimal area
LA = left atrial
LGC = lateral gain control
LVMI = left ventricular mass index
tau = time constant of relaxation
TGC = time gain compensation
Δt = time from the P wave to the maximal pressure/area ratio

Methods

Study patients. The study included 25 patients in whom the LA pressure–area relation was assessed, and the effect of inotropic stimulation of LA function was studied. Eleven patients had atypical chest pain and no evidence of heart disease after a complete clinical, electrocardiographic, echocardiographic and hemodynamic workup. Seven patients with an enlarged LA (maximal LA diameter >4 cm as derived from the M-mode echocardiogram) resulting from heart failure due to ischemic heart disease were also included in the study cohort. The diagnosis of heart failure due to coronary artery disease was based on the following criteria: New York Heart Association functional class III; angiographic left ventricular dilation (end-systolic area index ≥28 cm^2/m^2), significant wall motion abnormalities and left ventricular ejection fraction <0.35; coronary artery disease in at least one of the major coronary arteries, with a ≥70% diameter stenosis; absence of valvular or congenital heart disease. The remaining seven patients had lone atrial fibrillation and were otherwise completely healthy. They were included in the study cohort if they were found to have a rest heart rate 65 to 95 beats/min without medications.

In an additional 10 patients randomly selected from those undergoing cardiac catheterization at our laboratory, the repeatability for obtaining the pressure–area relation was investigated (see Repeatability of the method).

In all patients, medications other than diuretic drugs and sublingual nitroglycerin, which were allowed as clinically indicated, were discontinued 5 half-lives before the study. LA cavity and walls were adequately visualized from conventional apical four-chamber echocardiographic views. This criterion was met in 35 of 37 patients initially screened. The research protocol was approved by the ethics committee of the institutional review board of the Department of Cardiology, Hippokration Hospital, Athens Medical School. Written informed consent was obtained from each subject after a detailed description of the procedure.

Echocardiographic study. Echocardiographic examination was carried out by the same expert operator (E.T.) using commercially available equipment (Hewlett-Packard Sonos 2500) with a 2.5-MHz transducer and an ABD application. Each subject was placed in a semirecumbent position, and two-dimensional imaging was performed using the conventional parasternal long-axis and apical four-chamber views. Transmitral Doppler flows were recorded by placing the sample volume at the tip of the mitral valve leaflets to obtain the highest velocity in early diastole (E wave) and the velocity at atrial contraction (A wave). The presence of left ventricular hypertrophy was assessed by two-dimensional and M-mode echocardiography using the American Society for Echocardiography standards (14).

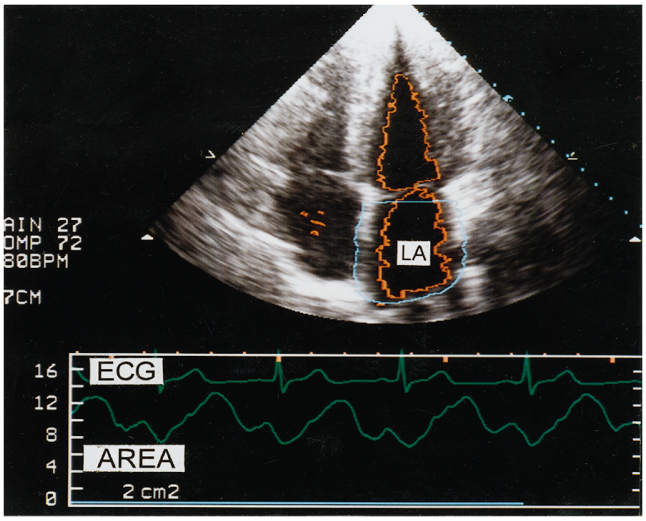


Figure 1. Echocardiographic ABD image (**top**), with the region of interest drawn around the left atrium (LA) and the instantaneous cavity area displayed simultaneously with the electrocardiogram (ECG), (**bottom**).

Thereafter, patients were placed in the supine position for simultaneous recordings of LA area and atrial and ventricular pressures. After obtaining the best possible two-dimensional image of the left atrium with the optimal gain and compress, ABD echocardiography was engaged. Lateral gain control (LGC) allowed the two-dimensional image to be the same as the regular two-dimensional image when ABD borders were turned off. Time gain compensation (TGC) adjusted the gain horizontally across a given depth of the image. Using LGC and TGC, the gain of the ultrasound left atrium was adjusted in small, precisely selected sectors allowing increased attenuation of ultrasound signals in myocardial tissue without affecting gain in the blood pool (12,13). To generate a region of interest that accurately conforms to the blood pool, a circle or half-ellipse was positioned around left atrium, and the system quickly and automatically generated a region of interest. Then, we automatically proceeded to on-line graphical display of the instantaneous LA area (in cm^2) (Fig. 1). A special effort was made to measure the LA area from exactly the same position during repeated measurements. This was achieved by directing the LA area to the position where the tracing of the region of interest was kept constant. All measurements were made at end-tidal volume apnea.

Comparison of ABD and conventional imaging-derived area. In a separate group of 29 patients (mean [±SD] age 50 ± 11 years) with adequately visualized LA walls, only the echocar-

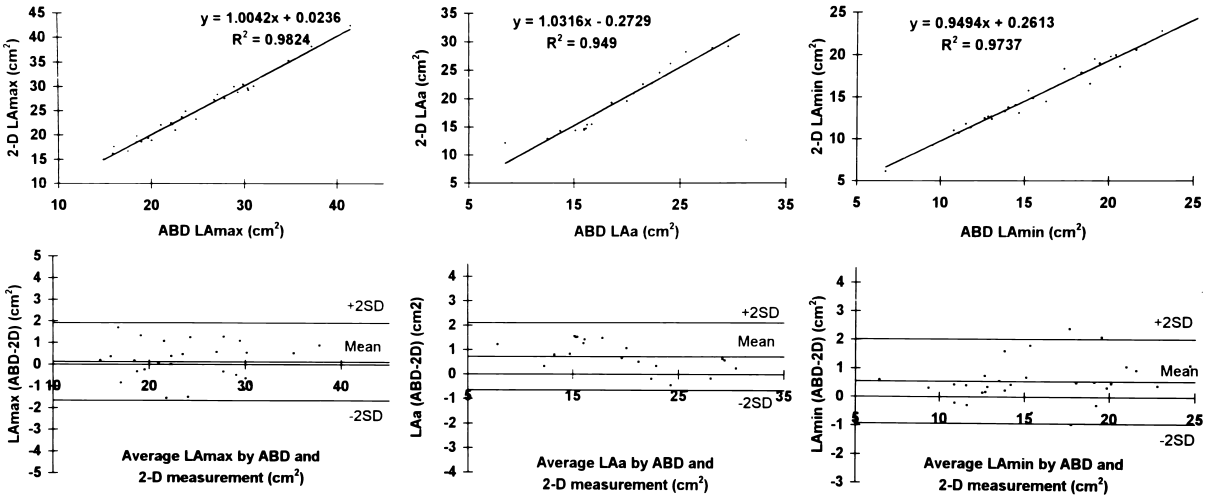


Figure 2. Top, Plot showing excellent correlations between ABD and two-dimensional (2-D) echocardiographic measurements of the LA area (maximal [LAmax], at onset of atrial systole [LAa] and minimal [LAmin]). **Bottom,** Graph showing difference between ABD and two-dimensional measurements of LA area versus their mean value. This figure demonstrates that there is a high degree of agreement between the two methods of measuring LA area.

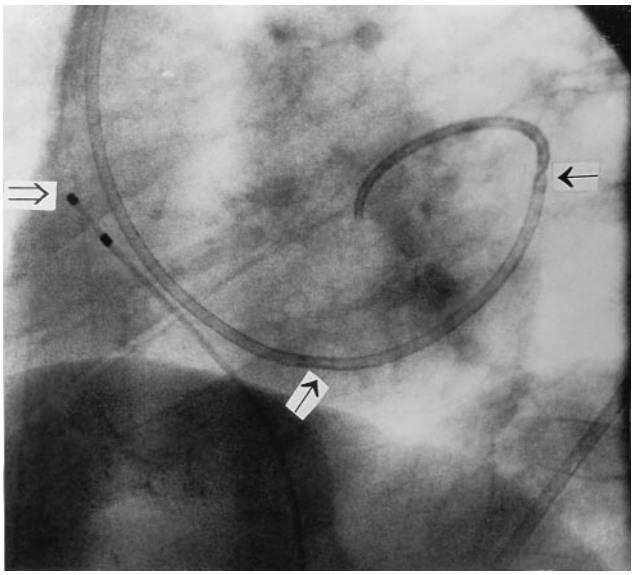
diographic studies (and not retrograde LA catheterization [see later]) were performed for validation of ABD-derived LA areas. In these patients, we compared the ABD-derived LA area with the established conventional off-line measurements of two-dimensional echocardiographic images (12,13). Sinus rhythm was present in 22 patients, and the remaining 7 were in atrial fibrillation. Apart from patients with normal two-dimensional echocardiograms, patients with essential hypertension, wall motion abnormalities, valvular heart disease and dilated cardiomyopathy were included.

LA maximal areas (measured at the point of mitral valve opening), LA minimal areas (measured at the point of mitral valve closure) and LA areas at onset of atrial systole (measured at the peak of the P wave in the simultaneously recorded electrocardiogram only in patients with sinus rhythm) obtained instantaneously by ABD were compared with the areas measured off-line by planimetry of the conventional echocardiographic images using nonsimultaneous beats (Fig. 2). For comparisons, 5 beats were averaged.

Retrograde LA catheterization. After all patients had received premedication with diazepam (5 mg intramuscularly), selective coronary angiography and left ventriculography were performed through the right femoral artery using an 8F sheath. The angiographic studies were evaluated by two observers (C.S., C.T.) in blinded manner.

All patients received 10,000 U of intravenous heparin before retrograde LA catheterization. A 7F Millar double-tipped micromanometer (model 804-8169, pigtail), with the sensors 7 cm apart, was used for pressure measurements. The transducers were calibrated electronically against mercury at the beginning of each study. Retrograde LA catheterization was performed according to our usual practice, as previously reported (9–11). By means of a steerable LA catheter (Stefanadis-Toutouzas, Special product, 5RE-699 by Cordis Europa), a guide wire was advanced into the left atrium under continuous fluoroscopy. Thereafter, the steerable catheter was withdrawn, and the Millar catheter was passed over the guide wire and introduced into the left atrium. The distal sensor was located in the left atrium and the proximal sensor in the left ventricle. A pacing wire was positioned in the high lateral right atrial wall for atrial pacing through a right femoral vein sheath (Fig. 3).

Figure 3. Left lateral view of a radiographic image of the pigtail Millar catheter (which was inserted retrogradely) and the pacing wire. **Solid arrowheads** indicate the two tips of the micromanometers in the left atrium and left ventricle, respectively; **open arrow** points to the tip of the pacing wire in the high lateral right atrial wall.



Study design. *Baseline measurements.* In all patients, baseline measurements were recorded at rest, during a steady state period, 30 min after the last infusion of contrast medium.

Altered contractile state. Dobutamine was administered through a peripheral intravenous line in graded doses. Administration protocol included a starting rate of 5 μg/kg body weight per min and an increase in the dose by 5 μg/kg per min every 3 min to a maximum of 40 μg/kg per min, if needed, to achieve the end-points. The end points for intravenous dobutamine administration were prespecified and included heart rate 20 beats/min above the rest heart rate or development of intolerable symptoms. To reach these end points, the average duration of the infusion was 6.1 ± 1.1 min in normal subjects, 6.3 ± 1.2 min in patients with atrial fibrillation and 12.5 ± 3.3 min in patients with heart failure. After reaching the end points, the dobutamine infusion was discontinued, and hemodynamic values were allowed to return to baseline. After 30 min, measurements were repeated with right atrial pacing at a heart rate equal to that achieved by dobutamine infusion. Thus, the possible effect of heart rate on LA function was overcome in subsequent comparisons between variables at dobutamine administration and at pacing after dobutamine discontinuation. The duration of the research protocol did not exceed 60 min.

In patients with atrial fibrillation, a cardiac cycle at dobutamine administration was accepted for comparison with the rest condition if the cycle duration deviated <2% from the median cardiac cycle in the sampling period, which consisted of 10 consecutive cardiac cycles, and if the left ventricular pressure amplitude of that cycle exceeded 95% of the maximum value obtained during the same period. The average of three such cycles were compared with the average of three cycles at the same duration at rest condition.

Repeatability of the method. To test the repeatability of this method, we investigated six men and four women, randomly selected, with a mean age of 53 ± 10 years. These patients were investigated at two separate times. Seven patients had coronary artery disease, five had a history of remote myocardial infarction, and two had congestive heart failure (functional class III). The repeatability coefficient was calculated as defined by the British Standard Institution (15).

Data collection. Millar micromanometer and electrocardiographic cables were connected to a VF-1 mainframe (Crystal Biotech). Signals of LA and left ventricular pressures, as well as signals of LA area and the electrocardiogram, were fed into a personal computer (IBM Pentium, 100 MHz) and simultaneously displayed in real-time mode on the monitor of the computer using a multichannel 12-bit analog to digital converter (Data Translation Inc.) and commercially available data acquisition software (Dataflow, Crystal Biotech), as previously reported (16). The sampling rate was 3 ms. Plots of simultaneous pressure and area were obtained using a commercially available software (Microsoft Excel for Windows) (Fig. 4).

Data analysis. The stored digitized data were analyzed by computer algorithm. For LA pressure and area values and subsequent calculations of derivative variables analyses were performed for 10 consecutive cycles in patients with sinus rhythm or 3 representative cycles in patients with atrial fibrillation, and the results were averaged. The LA pressure–area curve was obtained at baseline, at pacing and after dobutamine administration (Fig. 5).

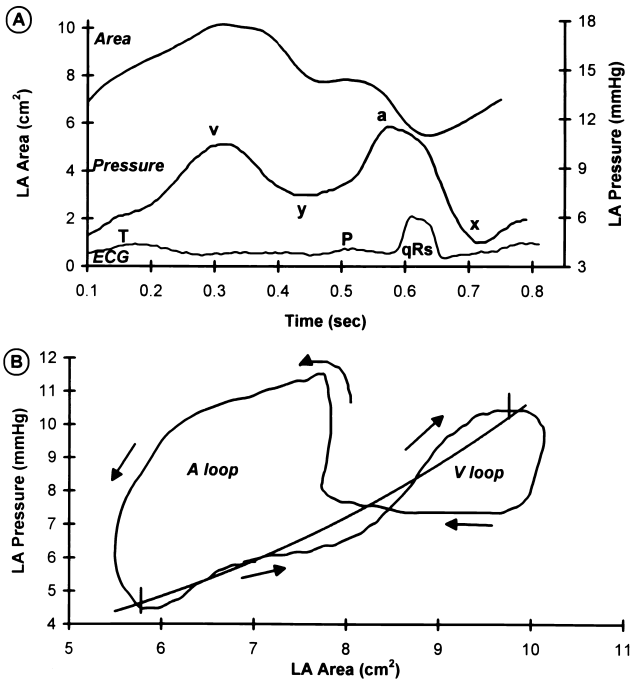


Figure 4. A, LA area and simultaneous LA pressure and electrocardiogram (ECG). **B,** The LA pressure–area relation comprises two loops: the A loop, expressing the LA pump function, and the V loop, expressing the reservoir function of the left atrium. During the filling period, the curve is directed upward and to the right, and after maximal pressure and area of the filling period have been reached, the curve turns clockwise and downward, corresponding to the passive emptying and, subsequently, active emptying phases.

There was a delay of the ABD image depending on the depth at which the echocardiographic study was performed and on the rate of sweep of the ABD image (17). Thus, a correction (equal to 2d/v + t + 1/f, where d = depth of examination; v = velocity of sound; t = flyback time; and f = sweep frequency) for area data was made. In the 25 study patients (11 normal subjects, 7 patients with heart failure, 7 patients with atrial fibrillation) and in the 10 repeatability group patients, this correction was validated by correlating the delay calculated by the above formula against the delay calculated from the time interval between minimal LA ABD area and the peak of the QRS complex of the digitized electrocardiogram. The correlation was excellent (r^2 = 0.98, slope 1.02), and the mean difference between the two methods was 1.3 ms (95% confidence interval 0.1 to 2.4).

Left ventricular variables. The left ventricular high fidelity pressure contours were analyzed by the Excel for Windows computer software. The following measurements and calculations were performed: maximum rate of rise of left ventricular

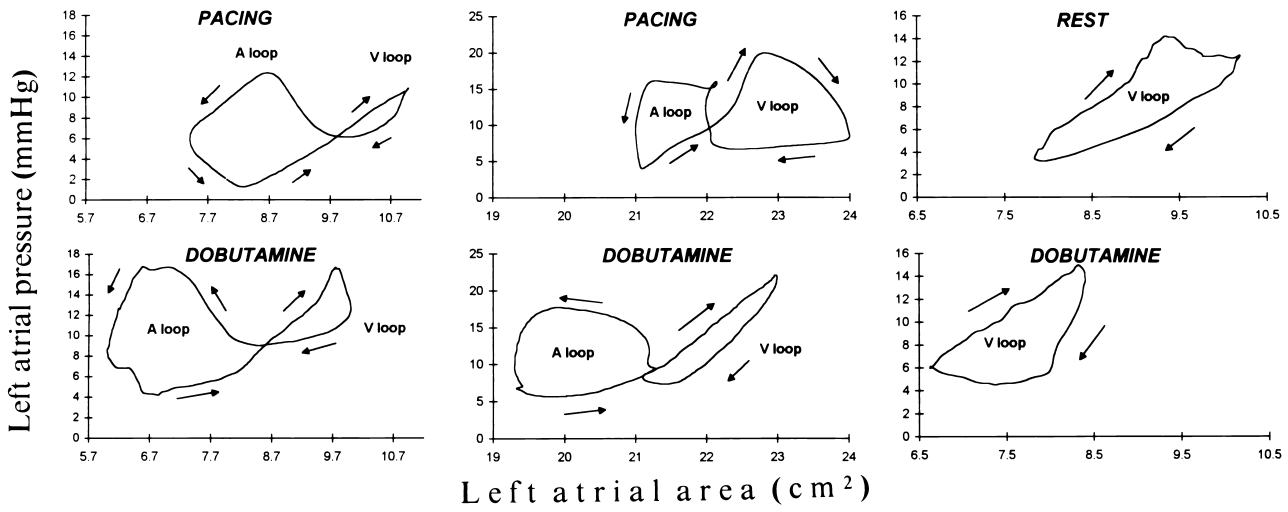


Figure 5. Representative LA pressure–area loops during pacing and dobutamine administration in a normal subject (**left**) and a patient with heart failure (**middle**), as well as during rest and dobutamine administration in a patient with atrial fibrillation (**right**).

systolic pressure (peak +dP/dt), left ventricular end-diastolic pressure, peak systolic blood pressure and time constant of relaxation (tau). Tau was calculated by the semilogarithmic method, allowing the pressure to decay to a zero asymptote P_B: $P_{(t)} = P_0 e^{-t/tau}$. A nonlinear (18) least squares technique was used to estimate the tau. For the high fidelity pressure curve, the nonlinear least squares fit was begun at minimal dP/dt and ended at 5 mm Hg above the left ventricular end-diastolic pressure. From the parasternal long-axis view using two-dimensional echocardiography, the left ventricular mass index (LVMI) was calculated (19).

LA function. TIMING OF ATRIAL CONTRACTION. From the digitized data, the PR electrocardiographic interval and the time interval from the onset of the P wave to the maximal ratio of LA pressure to LA area (Δt) were measured.

PRESSURE–MINIMAL AREA RELATION. Least squares linear regression analysis was applied to nonisochronal pressure–normalized area points at the time of LA end-systole; instead of absolute area, the normalized area calculated by the formula $A - A_{mean}$ (where A_{mean} is the average minimal LA area of each group) was used to normalize the slope of the pressure-minimal area relation to the differences in LA size in the different groups (20,21). The slope of this linear fit and the normalized area axis intercept of the same regression line were calculated both at pacing and after dobutamine administration in all patients. For each patient, the minimal LA area was taken at end-systole (Fig. 6).

LA WORK INDEXES. The area of the A loop (the first counterclockwise loop of the total LA pressure–area curve) and the V loop (the second clockwise loop) was measured (Fig. 4 and 5). The LA stroke work index, expressing the booster pump function, was defined as the area of the counterclockwise A loop (5,7,22).

LA SYSTOLIC EMPTYING INDEX. The ABD-derived LA area at onset of LA systole measured at the peak of the P wave in the simultaneously recorded electrocardiogram (A_a) and end-systolic area (A_{min}) were used to compute the LA systolic emptying index, which was defined as the ratio of $(A_a - A_{min})/A_a$ (12,13).

LA PEAK RATES OF ATRIAL SYSTOLIC SHORTENING AND ATRIAL FILLING. The digitized ABD-derived LA area data were used to compute LA peak rates of atrial systolic shortening and filling index that were defined as the absolute first derivative of LA area change (dA/dt) during passive shortening, active shortening and the filling phase.

LA STIFFNESS. The elastic characteristics of the LA chamber were assessed by the pressure–area relation corresponding to the period from the nadir of the x wave of LA pressure to the peak of the V wave. Pressure and area data during this period of the clockwise ascending limb of the pressure–area loop were then fitted to the exponential function $P = bxe^{\alpha \cdot A}$, where P = instantaneous LA pressure; and A = LA area (Fig. 4). The least squares method was used for calculation of α and b, where α is the passive elastic chamber stiffness constant (cm^{-2}) that determines the slope of the exponential curve (23), and b is the elastic constant (mm Hg).

Statistical analysis. Continuous variables were compared using the Student paired or unpaired *t* test for repeated measures when appropriate. Correlations between variables were calculated using standard linear regression analysis. The slope and axis intercept of the normalized pressure–minimal area relation, as well as the slope and axis intercept of the relation between the A loop and the LA area at the beginning of LA shortening from repeated measurements, were compared using two-way repeated measures analysis of covariance (SPSS, 7.0 version, for Windows). The Bland-Altman method (24) was used to compare the ABD-derived LA areas with LA areas obtained by the conventional two-dimensional images. A p value <0.05 was considered statistically significant. Results are expressed as mean value ± SD.

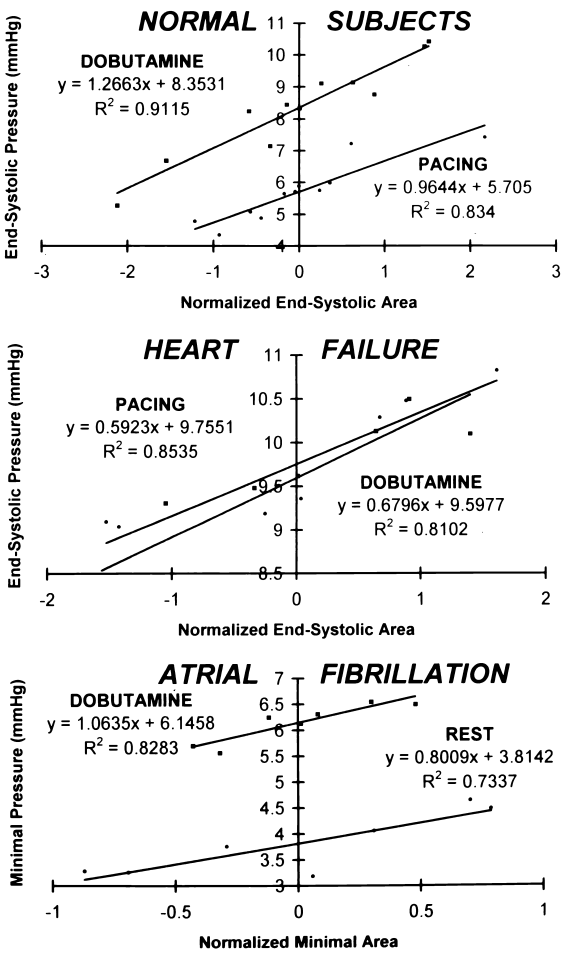


Figure 6. Linear regression lines derived from isochronal pressure–area points at end-systole during pacing in normal subjects and patients with heart failure and during rest in patients with atrial fibrillation, as well as during dobutamine administration in all patients. There was an increase in the slope of the pressure–area relation due to inotropic stimulation.

Results

Validation of ABD-derived LA area. Correlation of the areas of the ABD method with those of conventional two-dimensional echocardiography was excellent for LA maximal areas (r^2 = 0.98, slope 1.004), LA areas at onset of atrial systole (r^2 = 0.95, slope 1.032) and LA minimal areas (r^2 = 0.97, slope 0.949). The mean difference between the two methods was 0.128 cm^2 (95% confidence interval −1.662 to 1.918) for LA maximal areas, 0.731 cm^2 (95% confidence interval −0.639 to 2.102) for LA areas at onset of atrial systole, and 0.546 cm^2 (95% confidence interval −0.927 to 2.019) for LA minimal areas (Fig. 2).

Repeatability of the method. Repeatability coefficient values for intraobserver repeatability (comparison of two determinations obtained at 20-min intervals, representing repeated measurements by the same observer) concerning LA area and pulsatile changes were 0.86 and 0.29 cm^2, respectively. These values were small compared with the mean values of LA area and its pulsatile changes in this sample (15 and 3 cm^2, respectively). The same procedure was applied for LA pressure at the peak of the A wave, stroke work index and stiffness constant. Repeatability coefficient values for pressure, stroke work index and stiffness constant were 0.4 mm Hg, 1.1 mm Hg·cm^2 and 0.005 cm^{-2}, respectively. These values were small compared with the mean values of LA pressure, stroke work index and stiffness constant in this sample (13.25 mm Hg, 15.3 mm Hg·cm^2, 0.196 cm^{-2}, respectively).

Baseline measures. Subject characteristics, as well as hemodynamic and echocardiographic data, are summarized in Table 1. The diastolic performance of the left ventricle in patients with heart failure was impaired compared with that in normal subjects, whereas patients with lone atrial fibrillation did not differ from normal subjects with regard to left ventricular diastolic function indexes. Thus, compared with normal subjects, patients with heart failure had increased left ventricular mass index ($p < 0.001$) and tau ($p < 0.05$).

In patients with atrial fibrillation, the pressure–area relation comprised the V loop only (Fig. 5). In normal subjects, areas of the A loop were significantly greater than areas of the V loop (7.3 ± 1.9 vs. 1.8 ± 0.5 mm Hg·cm^2, $p < 0.001$). In contrast, in patients with heart failure the areas of the A loop were significantly smaller than the areas of the V loop (3.9 ± 0.8 vs. 6.7 ± 1.2 mm Hg·cm^2, $p < 0.001$). Furthermore, the area of the A loop was significantly less in patients with heart failure than in normal subjects ($p < 0.001$) (Fig. 5).

The LA systolic emptying index was significantly greater in normal subjects than in patients with heart failure (22.1 ± 5.2 vs. 5.3 ± 0.7%, $p < 0.001$).

LA pressure–area relations during the atrial filling phase fitted the exponential function closely. The correlation coefficient (r) ranged between 0.89 and 0.99. In normal subjects, in patients with heart failure, and in patients with atrial fibrillation, the passive elastic chamber stiffness constant was 0.623 ± 0.107, 0.801 ± 0.097 and 0.796 ± 0.091 cm^{-2}, respectively (Table 1).

Effects of altered inotropic state. *Hemodynamic changes.* In all patients, elevation of heart rate of 20 beats/min above rest values was achieved. No patient developed intolerable symptoms. Changes in systolic and diastolic blood pressures, maximal dP/dt, left ventricular end-diastolic pressure, E/A ratio and tau are shown in Table 2. In all subjects in sinus rhythm (11 normal subjects, 7 patients with heart failure), dobutamine significantly reduced the PR interval (by 17.0 ± 2.7%) and Δt (by 22.1 ± 1.2%) compared with atrial pacing (PR interval: dobutamine 140.3 ± 16.2 vs. pacing 169.5 ± 22.7 ms, $p < 0.001$; Δt: dobutamine 125.5 ± 19.5 vs. pacing 161.2 ± 25.8 ms, $p < 0.001$). A positive correlation between percent changes in PR interval and Δt was found (Fig. 7).

LA size, LA systolic emptying index and peak rate of atrial systolic shortening and atrial filling. After dobutamine administration, maximal and minimal LA area were significantly decreased in all groups (Table 2). Moreover, the pulsatile changes in LA area were decreased in normal subjects and in patients with heart failure (Table 2).

Table 1. Patient Characteristics and Hemodynamic Data at Rest

	Normal Subjects (n = 11)	Pts With HF (n = 7)	Pts With AF (n = 7)
M/F	7/4	4/3	4/3
Age (yr)	54.3 ± 6.1	53.8 ± 6.5	55.1 ± 6.4
LV wall thickness (mm)	17 ± 5	12 ± 4*	19 ± 5
LV mass index (g/m^2)	92.5 ± 15.1	130.1 ± 16.0†	93.1 ± 15.8
Heart rate (beats/min)	71.7 ± 5.9	72.3 ± 6.4	79.2 ± 7.4‡
Systolic BP (mm Hg)	118 ± 10	122 ± 11*	121 ± 9
Diastolic BP (mm Hg)	75 ± 6	79 ± 10	78 ± 8
LV variables			
LVEF (%)	65 ± 8	25 ± 5†	65 ± 7
LVEDP (mm Hg)	8.7 ± 2.5	16.3 ± 4.2†	9.2 ± 3.8
dP/dt_{max} (mm Hg/s)	1,432 ± 196	805 ± 177†	1,297 ± 201
Tau (ms)	31 ± 5	40 ± 7*	32 ± 5
Peak E wave (cm/s)	57 ± 8	64 ± 9	68 ± 7‡
Peak A wave (cm/s)	48 ± 7	41 ± 5*	—
E/A ratio	1.2 ± 0.3	1.5 ± 0.4	—
LA variables			
Maximal LA area (cm^2)	11.2 ± 3.5	24.3 ± 5.1†	10.9 ± 4.1
LA area at onset of atrial systole (cm^2)	10.4 ± 3.2	22.8 ± 4.9†	—
Minimal LA area (cm^2)	8.1 ± 2.9	21.6 ± 4.7†	8.3 ± 3.6
LA systolic emptying index (%)	22.1 ± 5.2	5.3 ± 0.7†	—
P_A (mm Hg)	11.8 ± 3.8	15.1 ± 6.3	—
P_V (mm Hg)	10.1 ± 3.4	18.8 ± 6.9‡	13.9 ± 2.7*
A loop (cm^2·mm Hg)	7.3 ± 1.9	3.9 ± 0.8†	—
V loop (cm^2·mm Hg)	1.8 ± 0.5	6.7 ± 1.2†	6.8 ± 0.9†
LA chamber stiffness constant (cm^{-2})	0.623 ± 0.107	0.801 ± 0.097‡	0.796 ± 0.091‡

*$p < 0.05$, †$p < 0.001$, ‡$p < 0.01$, patients (Pts) with heart failure (HF) and atrial fibrillation (AF) versus normal subjects. Data presented are mean value ± SD or number of patients. A loop = area of A loop; BP = blood pressure; dP/dt_{max} = maximal rate of rise of left ventricular (LV) pressure; F = female; LA = left atrial; LVEDP = LV end-diastolic pressure; LVEF = LV ejection fraction; LV wall thickness = sum of posterior LV wall and ventricular septal thickness; M = male; P_A = LA pressure at peak of A wave; P_V = LA pressure at peak of V wave; Peak E and A = peak transmitral blood flow velocity during early and late diastole, respectively; Tau = LV time constant of relaxation; V loop = area of V loop; — = no data.

After dobutamine administration, the LA systolic emptying index was significantly increased in both normal subjects ($p < 0.05$) and in patients with heart failure ($p < 0.001$) (Table 2). Peak filling rate increased in patients with heart failure ($p < 0.05$), normal subjects ($p < 0.001$) and patients with atrial fibrillation ($p < 0.001$) (Table 2). The absolute peak passive emptying rate increased in normal subjects ($p < 0.001$) and in patients with atrial fibrillation ($p < 0.001$) but decreased in patients with heart failure ($p < 0.05$) (Table 2). The absolute peak active emptying rate increased in both normal subjects ($p < 0.001$) and patients with heart failure ($p < 0.05$).

LA pressure–area relation, work indexes and stiffness. Figure 6 illustrates the pressure–minimal area lines derived from the linear fits of pressure–area data at LA end-systole during pacing (or at rest in patients with atrial fibrillation) and after dobutamine infusion. Increased inotropic state resulted in an increase in the normalized slope (by 32.3% in normal subjects, $p < 0.01$; 15.3% in patients with heart failure, p = NS; 32.5% in patients with atrial fibrillation, $p < 0.05$). The intercept remained unchanged in normal subjects and in patients with heart failure. In patients with atrial fibrillation, the intercept was significantly increased after dobutamine administration (Table 2). Moreover, a leftward shift in pressure–area trajectory was observed after dobutamine administration in all groups (Fig. 5).

After dobutamine infusion, both areas of the A and V loops were significantly increased in normal subjects ($p < 0.001$). In patients with heart failure, the area of the A loop was significantly increased, whereas the area of the V loop was significantly decreased ($p < 0.001$). Finally, in patients with atrial fibrillation, there was no change in the V loop (Table 2, Fig. 5).

A positive correlation between the area of the A loop and LA area at the beginning of LA shortening was found in both normal and failing hearts (Fig. 8). An increase in the slope of the regression line was detected after dobutamine administration compared with that after atrial pacing in both normal subjects and patients with heart failure ($p < 0.001$ for both).

The slope of the monoexponential curve expressing the passive elastic stiffness constant was significantly decreased in all patients ($p < 0.001$ for all) (Table 2).

Discussion

The results of the present study indicate that the combined measurements of LA pressure, obtained from a catheter-

Table 2. Hemodynamic Variables After Dobutamine Administration

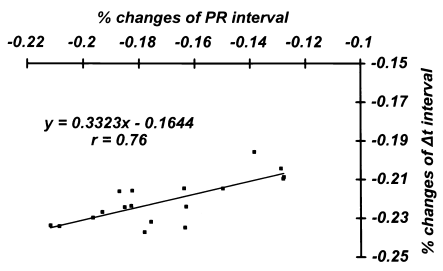
	Normal Subjects		Pts With HF		Pts With AF	
	RAP	Dob	RAP	Dob	Rest	Dob
Heart rate (beats/min)	92.5 ± 6.7	92.3 ± 6.5	93.4 ± 7.5	93.1 ± 6.3	90.1 ± 9.7	90.4 ± 9.1
Systolic BP (mm Hg)	124 ± 10	145 ± 7*	128 ± 8	142 ± 12†	128 ± 13	144 ± 15†
Diastolic BP (mm Hg)	78 ± 8	86 ± 9†	73 ± 9	88 ± 10†	80 ± 7	85 ± 9
LV variables						
LVEDP (mm Hg)	10.1 ± 3.1	7.2 ± 1.8†	17.1 ± 3.1	15.0 ± 2.2	9.8 ± 1.9	8.4 ± 2.1
dP/dt_{max} (mm Hg/s)	1,659 ± 295	2,537 ± 301*	897 ± 144	1,117 ± 256	1,401 ± 227	2,489 ± 381*
Tau (ms)	28 ± 5	19 ± 3*	37 ± 9	35 ± 6†	32 ± 6	19 ± 5*
Peak E wave (cm/s)	54 ± 7	50 ± 8	59 ± 6	56 ± 7	66 ± 8	65 ± 7
Peak A wave (cm/s)	51 ± 6	53 ± 6	46 ± 6	47 ± 5	—	—
E/A ratio	1.1 ± 0.1	1.0 ± 0.1†	1.3 ± 0.2	1.2 ± 0.2	—	—
LA variables						
Maximal LA area (cm^2)	11.0 ± 2.9	9.9 ± 2.5*	23.9 ± 3.9	23.0 ± 2.7†	10.2 ± 2.0	8.3 ± 1.8‡
Minimal LA area (cm^2)	7.4 ± 2.4	5.7 ± 1.7*	21.0 ± 3.3	19.3 ± 2.4†	7.1 ± 1.3	5.0 ± 1.5†
Maximal LA area − minimal LA area (cm^2)	3.6 ± 0.6	4.2 ± 1.0†	2.9 ± 0.7	3.7 ± 0.8‡	3.2 ± 0.9	3.3 ± 0.8
P_A (mm Hg)	13.8 ± 2.7	15.1 ± 2.8	17.6 ± 2.5	16.2 ± 3.1	—	—
P_V (mm Hg)	11.6 ± 2.2	14.1 ± 2.6†	22.5 ± 4.1	20.1 ± 4.2	14.2 ± 2.4	14.9 ± 2.9
P_{mean} (mm Hg)	8.5 ± 1.7	10.0 ± 2.2	15.3 ± 2.7	12.5 ± 2.1†	9.1 ± 1.7	9.8 ± 1.8
LA systolic emptying index (%)	24.1 ± 5.4	29.4 ± 5.8†	5.0 ± 1.1	9.8 ± 1.2*	—	—
Peak filling rate (cm^2/s)	9.6 ± 1.5	14.2 ± 2.8*	9.0 ± 2.6	13.3 ± 2.9†	6.4 ± 1.2	9.3 ± 1.9*
Peak passive emptying rate (cm^2/s)	10.9 ± 2.0	18.6 ± 3.4*	16.3 ± 3.1	12.4 ± 2.3†	6.9 ± 1.3	−12.8 ± 2.1*
Peak active emptying rate (cm^2/s)	10.9 ± 2.1	14.5 ± 2.7*	9.5 ± 1.9	12.4 ± 2.4†	—	—
A loop (cm^2·mm Hg)	10.2 ± 0.9	13.8 ± 1.9*	4.3 ± 0.4	7.6 ± 0.4*	—	—
V loop (cm^2·mm Hg)	1.3 ± 0.1	2.8 ± 0.7*	7.3 ± 1.2	2.9 ± 0.1*	6.5 ± 1.3	5.3 ± 1.2
LA chamber stiffness constant (cm^{-2})	0.712 ± 0.141	0.473 ± 0.089*	0.896 ± 0.181	0.494 ± 0.093*	0.779 ± 0.145	0.467 ± 0.086*
Slope (mm Hg/cm^2)	0.96	1.27‡	0.59	0.68	0.80	1.06†
Intercept (cm^2)	5.71	8.35	9.76	9.60	3.81	6.15‡

*$p < 0.001$, †$p < 0.05$, ‡$p < 0.01$, atrial pacing (RAP) versus dobutamine (Dob) in normal subjects and patients with heart failure, or rest versus dobutamine in patients with atrial fibrillation. Data presented are mean value ± SD. Intercept = area axis intercept of left atrial pressure–minimal area relation; P_{mean} = left atrial mean pressure; Slope = slope of pressure–minimal area relation; other abbreviations as in Table 1.

tipped micromanometer introduced retrogradely into the atrium, and LA area, obtained simultaneously by ABD two-dimensional echocardiography, may provide a reliable and feasible determination of the LA pressure–area relation. By means of this method, it was found that the pressure–minimal area relation is highly linear and sensitive to changes in inotropic state. The LA stroke work index was accurately calculated, and good correlation was found with LA preload.

The present study also showed that LA pump function is reduced in patients with heart failure, whereas LA stiffness is increased in patients with heart failure and in those with atrial fibrillation. In addition, increased inotropic state after dobutamine administration resulted in improved LA pump function in normal subjects and in patients with heart failure as well as in decreased LA stiffness in all patient groups.

Figure 7. Correlation of percent change in Δt (dobutamine vs. pacing) with the percent change in PR interval (dobutamine vs. pacing).



Pressure–minimal area relation. Because of the relative simplicity of its derivation, elastance at minimal area (E_m) is most often used as an index of LA contractility, reflecting basal LA contractile function (20,21). Determination of the end-systolic pressure–area relation requires alteration of load and an ensemble of end-systolic pressure–dimension points for each subject; in the present study, each patient contributed a single pressure–area point to the regression. Thus, the slope of the end-systolic pressure–area relation represents the elastance of the group of patients, not the elastance of each patient within the group.

In the present study, increased inotropic state was associated with an increased slope of pressure–minimal area relation in normal subjects and in patients with atrial fibrillation, whereas no significant changes were observed in patients with heart failure. Moreover, acute right or left parallel shifts of the end-systolic pressure–area relation without changes in the slope may also indicate a decline (or improvement) in contractile performance (25). In our study, in addition to the increases in the slopes of the pressure–minimal area relations, we found that in normal subjects and in patients with atrial fibrillation,

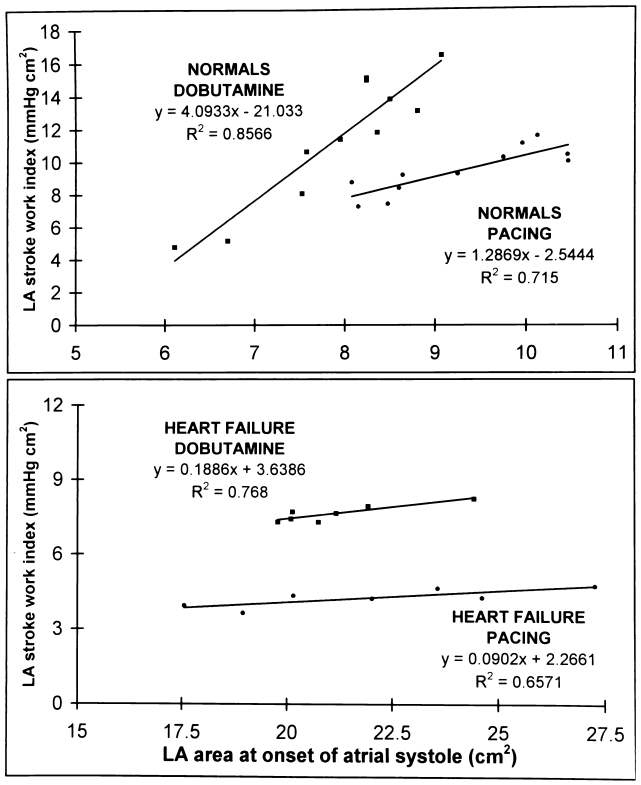


Figure 8. Relation between LA area at the onset of atrial systole and LA stroke work index in patients with sinus rhythm. The regression line for atrial pacing and dobutamine is shown. In both groups there is an increase in the slope after dobutamine administration; however, this increase is less in patients with heart failure than in normal subjects.

dobutamine infusion resulted in immediate leftward parallel shifts of the pressure–minimal area relation (Fig. 6).

The mechanism of the increase in the slope of the LA pressure–minimal area relation by dobutamine administration in patients with atrial fibrillation is not clearly defined. One possibility is improved left ventricular systolic performance associated with rapid reduction in LA afterload after dobutamine administration. This function reflects a passive rather than active process of the left atrium correlated to left ventricular systolic performance.

Pump function and Frank-Starling mechanism in left atrium. The LA stroke work index represents an estimation of total atrial work, which is the sum of energy expended to accelerate blood toward the left ventricle, along with the energy required for the small transient reversal of pulmonary venous flow. In the present study, an increased inotropic state in the same level of heart rate resulted in an increase in LA stroke work index. Moreover, the leftward shift of the A loop indicated a positive inotropic effect of dobutamine on LA systole. The changes in LA stroke work index were similar to those of the LA systolic emptying index and peak active emptying rate, which could serve as noninvasive indexes of LA pump function.

In contrast to our results, Hoit et al. (26) reported that in pacing-induced heart failure in dogs, the A loop area was significantly greater than that in control dogs. This compensatory increase in the LA component of left ventricular filling, which was absent in our patients with congestive heart failure, may be due to the different stage of left ventricular dysfunction. It has been reported (27) that with increasing severity of left ventricular dysfunction, different patterns of left ventricular diastolic filling emerge, and the LA contribution to left ventricular filling gradually decreases. The loss of this compensatory action and the subsequent decline in the LA contribution to ventricular filling may reflect increased work load imposed on the LA myocardium, which, over time, can lead to LA dilation and intrinsic LA dysfunction. Furthermore, the canine model that was used in the study of Hoit et al. (26) has many dissimilarities with our patients in whom heart failure resulted from loss of viable myocardium. Other possible explanations for the difference between the previous canine and present human results include species differences, concomitant diseases, medical treatment and a variety of genetic and environmental factors. However, it cannot be excluded that small LA stroke work in patients with congestive heart failure does not reflect failing contractile performance, but it is the result of the increased afterload.

One interesting difference between the atrial pacing and dobutamine infusion are the values of PR and Δt, which both shorten after dobutamine infusion. However, this decrease was larger in Δt than in the PR interval. Thus, ample time is left for the atrial "kick" to boost ventricular filling during the fairly short period that is defined by the PR interval (21). Moreover, because early closure of mitral valve when the PR interval is short may result in impaired LA emptying, shortening of Δt with inotropic stimulation may protect against increased atrial stretch (28).

The LA area at the beginning of LA contraction could be considered as a preload for the LA active ejection. As shown in Figure 8, the LA stroke work index (the area of the A loop) was proportional to the LA area at the beginning of active atrial shortening. This indicated that the active external work of the LA depended on the LA preload, suggesting that the Frank-Starling mechanism might be operative in the human LA (7,22). After dobutamine administration, the slope of the relation increased, showing sensitivity to changes in inotropic state.

LA filling and passive emptying. It has been reported (6) that using the slope of the calculated linear pressure–area curve instead of a monoexponential curve fitting as an index of LA stiffness may create conflicting results. Therefore, in the present study, an exponential regression analysis was preferred for calculation of LA stiffness despite a good R value of linear fit. As indicated by the changes in this slope, patients with heart failure and with atrial fibrillation had an increased atrial stiffness compared with normal subjects. Moreover, in all patients, a reduction in LA stiffness was found after dobutamine infusion. This reduction may in part be due to an increase in LA area pulsatile changes. In addition, in all patients the increased peak LA filling rate may be attributed to improved LA elastic properties.

The V loop consisted of an ascending limb representing part of the filling phase and a descending limb representing part of the passive emptying phase. Peak passive emptying rate increased in normal subjects after dobutamine administration, whereas it decreased in patients with heart failure. Dobutamine administration resulted in increased LA mean pressure in normal subjects, whereas LA mean pressure decreased in patients with heart failure. In addition, dobutamine administration resulted in improvement of left ventricular relaxation. Thus, it can be speculated that the peak passive emptying rate is determined mainly by LA and left ventricular hemodynamic variables.

Specific comments. By using retrograde LA catheterization we avoided complications inherent to the alternative transseptal procedure, and, moreover, we had the advantages of assessing an intact LA chamber, thus avoiding any possible wall dysfunction due to transseptal catheterization. Retrograde nontransseptal LA catheterization is a well established method, applied in large series of patients in our laboratory as well as in other laboratories, without any serious complications (11,29). Furthermore, no functional (not even trivial) mitral regurgitation was observed as the Millar catheter was passed through the mitral valve leaflets (9). The method described here, although invasive, may prove helpful in studies of physiology because it provides the unique opportunity of gaining insights into LA function and the effect of pharmacologic agents.

ABD two-dimensional echocardiography, as a new technique, needs a considerable learning phase. However, despite its shortcomings (12,13), this technique may provide improved indexes of LA function if specific instructions are taken into account.

In the present study, LA area was calculated only from the apical four-chamber view because it is impossible to have simultaneous recordings of two echocardiographic views. This is a limitation of the study because dimensional changes during atrial contraction may be dissimilar in different planes. However, this limitation is counterbalanced by identical methodology during measurements in different phases of the protocol.

It is possible that myocardial ischemia may develop in with congestive heart failure patients who had ischemic heart disease during infusion of dobutamine. Although we cannot exclude the development of myocardial ischemia that may have altered ventricular or atrial hemodynamic function, the improvement in systolic and diastolic left ventricular function, as well as the absence of symptoms of angina, at least reduces the possibility that left ventricular myocardium suffered ischemia.

When accepting the end-systolic pressure–area relation as a measure of contractile function for the left atrium, it should be recognized that variation in chamber geometry and size may affect this relation (25). In the absence of an established method for normalization, we used the mean area of each group, which characterizes the respective group. However, further work is needed to ascertain the most appropriate means of adjusting for differences in LA size.

When the heart rate is increased by pacing, the PR interval prolongs, whereas it shortens with dobutamine. Although the opposite behavior of Δt occurs in these two conditions, the timing of atrial systole may differ. Therefore, because the timing of atrial systole is a determinant of the effectiveness of atrial contraction, comparisons at matched heart rates obtained by these two interventions are inherently limited.

Clinical implications. There has been increasing interest in evaluating LA function during several conditions, such as dual-chamber pacing, left ventricular failure and atrial fibrillation. Because of the complexity of multiple interrelated factors contributing to LA function, conventional indexes are limited as a clinical tool for the evaluation of LA function. Our study suggests that approaches based on the pressure–area relation of the left atrium may be useful in describing LA contractile function in humans.

Assessing LA function in patients with congestive heart failure and atrial fibrillation is particularly important because different management may be needed on the basis of LA function. Furthermore, LA function in congestive heart failure and atrial fibrillation may be an important prognostic factor.

Conclusions. The method described in the present study provides accurate determination of the LA pressure–area relation. By means of this method, we found that LA pump function is reduced in patients with heart failure, whereas LA stiffness is increased in patients with heart failure and atrial fibrillation compared with that in normal subjects. Moreover, an increased inotropic state after dobutamine administration resulted in improved LA pump function in normal subjects and in patients with heart failure, as well as in decreased LA stiffness in all groups of patients.

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